as first site of recurrence. Thirty-seven percent of pts received taxol and 39% herceptin based regimens before cerebral relapse occurred. Among 81 pts with known hormone receptor status of their primary tumour, 42 (52%; 95%CI: 41–63%) had oestrogen and progesterone receptor negative tumours. C-erbB2 overexpression was identified in 38 of 78 assessed tumours (49%; 95%CI: 37–60%). These figures are significantly different from those expected in the general population of pts with breast cancer, where about 30% of cases are ER-/PgR-negative and roughly 25% show c-erbB2 overexpression ($p < 0.001$ for both comparisons, exact binomial test).
Conclusions: Pts with non endocrine responsive and Her-2/neu over-espressing disease may be considered at higher risk of brain relapse. In these subsets of pts screening and prophylactic measures should be investigated.

460 PUBLICATION

The significance of chemotherapy in the treatment of carcinomatous meningitis in breast cancer patients

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Introduction: Carcinomatous meningitis is a severe and progressive cancer metastasis caused by infiltration of the leptomeninges and the cerebrospinal fluid by cancer cells.
Purpose: The aim of the study was to establish if systemic chemotherapy applied after intrathecal treatment and radiotherapy can influence on survival period in patients with breast cancer carcinomatous meningitis.
Materials and methods: 53 patients with breast cancer and carcinomatous meningitis were treated in Cancer Center, Warsaw, between 1999–2005. Three methods of treatment were applied: intrathecal treatment, intravenous systemic chemotherapy and radiotherapy. Intrathecal methotrexate, 10 mg per dose, was performed in 89% patients. 30% did not respond after 1–2 courses of treatment and in these cases palliative treatment was continued. The others continued treatment. An average of 6 cycles (1–15) was administered; initially metothrexate twice a week and after clinical improvement the treatment was continued once a week until the normalization of the cerebrospinal fluid, however not more than 15 intrathecal injections.67% women received systemic chemotherapy concurrently with intrathecal treatment. Individual schedules of systemic treatment were used, but the most common were vinorelbine with fluorouracil, antracyclines, cisplatin, taxanes, trastuzumab and capecitabine. 59% patients received radiotherapy to the brain or spinal cord.
Results: Clinical and laboratory response was achieved in 67% patients. The mean survival since diagnosis of carcinomatous meningitis was 18 weeks (1–80 weeks).
In severe condition patients (Karnofsky <60%) who were not treated the median survival period was 4 weeks and after chemotherapy treatment was prolonged to 18 weeks. In not treated patients with Karnofsky above 60% the median survival period was 12 weeks. After systemic chemotherapy it was prolonged to 20 weeks. Log rank test stratified for Karnofsky status was highly statistically significant ($p < 0.001$).
Conclusions: Our observations suggest, that systemic chemotherapy added to intrathecal treatment and radiotherapy is an important factor improving survival in breast cancer patients with carcinomatous meningitis.

461 PUBLICATION

Long-term safety of intravenous ibandronate throughout 4 years of treatment for metastatic breast cancer

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Background: Despite their widespread use in metastatic bone disease, some intravenous bisphosphonates are occasionally associated with renal toxicity, which may lead to discontinuation of supportive care as well as anticancer medications. Ibandronate is a non-cyclic, single-nitrogen bisphosphonate with a renal safety profile comparable with placebo that is highly effective against skeletal complications and metastatic bone pain. Here, we present safety data from a study of intravenous ibandronate over a 4-year period.
Materials and methods: During an initial 2-year study, breast cancer patients with bone metastases (n = 62) were treated with placebo (n = 16) or ibandronate 6 mg (n = 46) by intravenous infusion over 1–2 hours every 3–4 weeks. In a 2-year extension phase, all patients received active treatment but were classified according to their initial treatment (placebo/6 mg and 6 mg/6 mg groups). Safety was assessed by adverse event (AE) reports and clinical laboratory evaluations. Data from the initial (Years 1–2) and extension (Years 3–4) phases of the study were analyzed separately.
Results: During the initial study, 56.3% of placebo- and 67.4% of ibandronate-treated patients reported treatment-related AEs, compared to 6.3% of the placebo/6 mg group and 13.0% of the 6 mg/6 mg group during the extension phase. All treatment-related AEs were either mild or moderate. Thirty-three patients experienced serious AEs overall (initial phase: placebo 31.3%, 6 mg 26.1%; extension: placebo/6 mg 18.8%, 6 mg/6 mg 28.3%). Withdrawals occurred during the extension phase (placebo/6 mg 12.5%, 6 mg/6 mg 8.7%), but none were due to renal AEs. Laboratory parameters of renal functioning remained normal and there were no clinically-relevant renal AEs throughout the extension phase.
Conclusions: Ibandronate had a good safety and tolerability profile throughout the 4-year study, with no serious AEs caused by the treatment. The absence of treatment-related renal AEs and lack of laboratory abnormalities suggests that the renal safety profile of ibandronate is better than other intravenous bisphosphonates.

462 PUBLICATION

Phase II trial of weekly paclitaxel (wP)+UFT for the treatment of patients with advanced breast cancer(ABC)

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Purpose: Phase II trials of combined chemotherapy for ABC using paclitaxel and 5-fluorouracil (Fu) have resulted in high response rates (50 to 60%) inspite of using as second line therapy following doxorubicin. Whereas wP has been reported for its effectiveness and usefullness, continuous administration of 5-Fu to maintain its plasma concentration (pc) needs hospitalization. We have already reported the effectiveness of addition of 5-Fu to wP, Phase I trial for wP+UFT orally, where the pc of 5-Fu is maintained by metabolic inhibition by uracil(ASCO 2002 Abs #1983). The recommended combination of wP+UFT for the treatment of patients with ABC is UFT 400 mg/body/day orally for 6weeks and P 80 mg/m^2 i.v. weekly for 6weeks of an 8-week cycle. A Phase II trial of wP+UFT for the treatment of patients with ABC is designed. The preliminary data of Phase II trial will be presented.
Methods: Patients with HER-2 negative, ABC without prior taxane in any setting were eligible. Patients were treated with or without Ps administered weekly for 6 weeks of an 8-week cycle. While the daily oral dose of UFT was fixed at 400 mg/body for 6 weeks, the dose of P was 80 mg/m^2 weekly as an hour infusion.
Results: A total of 21 patients were registered and randomized between 05/01 and 11/04, with 20 eligible for analysis(12 in wP+UFT, 8 in wP). The over all response rate(RR) is 65%. RR of wP+UFT and wP is 84.6% and 57.1% respectively. Ten patients were anthracycline pre-treated ABC. The most common reasons for discontinuation being progression/relapse (5%) and adverse events (5%). Grade 3 adverse events were 25%.
Conclusions: The combination of wP plus UFT is feasible alternative for the weekly paclitaxel therapy for advanced breast cancer.

463 PUBLICATION

Gemcitabine (GEM) plus oxaliplatin (LOHP) as salvage treatment in anthracycline and taxane pretreated patients with advanced breast cancer (ABC)

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Background: To evaluate the efficacy and toxicity profile of GEM and LOHP in women with ABC pretreated with anthracyclines and taxanes.
Methods: Patients with histologically confirmed and measurable breast cancer, pretreated with anthracycline- and taxane-based chemotherapy for advanced disease, ECOG PS $\leqslant 2$, and adequate bone marrow, renal and liver function, were eligible. Patients received GEM 1500 mg/m^2 on day 1 and 8 and LOHP 130 mg/m^2 on day 8 every 3 weeks until progression or unacceptable toxicity. Toxicity was evaluated in each cycle and response every 3 cycles.
Results: Between 3/2001 and 6/2004, 31 patients were enrolled and all were evaluable for toxicity and response. The median age was 63 (range 46–72) years. Eight (26%) patients had received 1 and 23 (74%) 2 prior chemotherapy regimens. Bone metastases were present in 11 patients, liver mets in 11 pts, lung mets in 17 pts and lymph node mets in 10pts; 17 (55%) pts had $\geqslant 2$ metastatic sites. A total of 127 cycles were administered (median 3 cycles; range, 1–9). Grade 3–4 neutropenia occurred in 14 (45%) pts, thrombocytopenia in 6 (19%) pts, and asthenia in 4 (13%) pts. CR was achieved in 1 (3%) and PR in 4 (13%) patients (ORR = 16%;

95%CI: 3.2–29.1%); nine (29%) pts had stable disease and 17 (54.9%) pts progressive disease. The median TTP was 4.6 months (range, 0.8–43.8) and the median OS 14.4 (range, 21–44.8) months.
Conclusions: The GEM/LOHP is a well tolerated and relatively active regimen for patients with heavily pretreated ABC, achieving a tumor growth control in 44% of the patients.

464 PUBLICATION

A pharmaco-epidemiological study of Trastuzumab therapy in metastatic breast cancer

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Introduction: A large pharmaco-epidemiological Brazilian study was conducted to investigate the efficacy, the treatment duration and the mostly prescribed treatments to patients with HER2 positive metastatic breast cancer (MBC).
Methods: Retrospective data was collected in 3 centers and statistical analysis was performed with a two-sided significant level of 5%. Treatment duration and disease-free survival were analyzed using the Kaplan-Meier method and were compared using a log-rank test.
Results: A total of 121 women range from 26 to 88 years (median = 53yo) with proven cancer breast were enrolled between may/2000 and november/2004. The HER-2 status (N = 110) was IHC 3+ = 93, IHC 2+ = 15, IHC 0–1+ = 2. Hormone receptor status (N = 121) was ER+ 47 and PR+ 36. The median time from diagnosis of primary disease to metastasic diagnosis was 2.2 years, range [0–7.8]. The median time from MBC diagnosis and the first prescription of trastuzumab was 159 days [0.0–2978]. 67% of patients used trastuzumab in first line, 21% in second line and 12% in third or others lines. The mostly used strategy therapy in the first-line was trastuzumab associated with vinorelbine (25.2%) and in the second-line were trastuzumab and paclitaxel (21.4%). In the whole population, the median DFS (defined as the time from initiation of trastuzumb to progression or death related to the disease) was 13.5 months, range 7 days to 4 years. CR was observed in 24.5%. No statistical difference on the treatment duration was found comparing patients who received his first course of trastuzumab on first or second-line ($p > 0.05$). The treatment duration in patients who received the first course of trastuzumab on first-line was much higher than among patients who received just on third-line and beyond ($p = 0.01$). The disease free survival for patients who received trastuzumab treatment in first-line was significant higher than patients who received his first course of trastuzumab on second-line ($p = 0.025$) IC: 94% and much higher than the group who received firstly on third and other lines (de $p < 0.0001$). No death was related to trastuzumab events.
Conclusion: We can conclude in this real-life model of analysis that trastuzumab shows greater benefits when used firstly in first-line, as we see in published randomized clinical trials results.

465 PUBLICATION

Male breast cancer: our experience from 1990 to 2004

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Male breast cancer (MBC) is a rare disease which accounts for less than 1% of all breast cancer cases. Approximately 400 new cases of MBC are diagnosed in Italy each year. We performed a retrospective analysis of 48 cases of MBC diagnosed since 1990, in order to analyse the pathological characteristics of the disease. The average age of these patients was 60 years (range 37–84). Forty-two patients had a diagnosis of ductal carcinoma; the others were: papillary 2, intraductal 2, lobular 2. High grade (G2-G3) tumors were present in 27 patients. Three patients were stage IV; 12 patients were stage III and 15 and 13 were stage II and I respectively; 36/48 (75%) patients were oestrogen or progesterone receptor positive, 4/48 (8%) patients were hormone receptor negative; in 8 patients oestrogen and progesterone receptors were not known. Thirty-one of the patients (65%) were treated with chemotherapy and anti-oestrogen therapy; 8 patients (17%) with anti-oestrogen therapy alone. Conservative surgery was performed in one patient only, while all the others underwent mastectomy (97%). Twenty (42%) had recurrences after treatment. Sites of relapse were: 8 visceral (17%), 5 bone (10%), 10 soft tissues (21%); local recurrence occurrence in 2 patients (4%).
BRCA1/2 mutational analysis was performed in 11 patients and two of them from high risk families, were identified as carriers of a BRCA2 mutation.
Conclusion: Thus, in our series, men with breast cancer are slightly younger, more likely to have hormone receptor positive disease, nodal metastases, and advanced stage disease than women with breast cancer. MBC patients should be offered genetic counselling and BRCA genetic testing when members of a high risk family.

466 PUBLICATION

A Phase II trial of gemcitabine (G) and doxorubicin (D) combination as first line treatment of metastatic breast cancer: preliminary results

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Methods: Previously untreated female patients (pts) with visceral metastatic breast cancer and ECOG PS $\leqslant 2$ were included. Pts received D 25 mg/m^2 and G 1250 mg/m^2 on days 1 and 8 for both drugs, every 21 days until progression or severe toxicity.
Results: 32 pts with a median age of 44.1 years (range: 29–67) were enrolled. All pts had stage IV disease. Metastatic sites are detailed in the table below. 31 patients were evaluable for toxicity and 26 patients for response. One patient has voluntary interrupted treatment after one cycle. After 178 cycles, grade 3 and 4 toxicity (WHO) were: neutropenia (4%), febrile neutropenia (0.5%), anemia (1.5%), nausea and vomiting (16%), diarrhea (2%), mucositis (11), reversible alopecia (56%). Among the 26 evaluable patients, response rates were: complete response 27% (7 pts), partial response 23% (6 pts), stable disease 8% (2 pts) and progression 42% (11 pts).

Metastatic sites

Metastatic sites	Number of pts	%
Liver	20	62.5
Lung	13	40.6
Bone	14	43.7
Lymph node	3	9.3
skin	1	3.1
*3 organs involved	2	6.25

Conclusions: The combination of GD in untreated metastatic breast cancer appears to be an active regimen with a safety toxicity profile. Further follow-up is necessary to assess the efficacy of this regimen.

467 PUBLICATION

Pegylated liposomal doxorubicin (PLD) plus cyclophosphamide as 1st-line therapy for metastatic breast cancer in patients previously treated with anthracyclines

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Background: Anthracyclines are among the most active drugs used for the treatment of breast cancer. Utilization in advanced disease however, is limited by their intrinsic dose limiting cardio-toxicity and extensive exposure in the adjuvant setting. Pegylated Liposomal Doxorubicin (Caelyx/Doxil) has been shown to possess similar activity to conventional doxorubicin, with a more favorable toxicity profile and significantly less cardiotoxicity. Cyclophosphamide is commonly used in combination with anthracyclines, thus represents an interesting drug to use with PLD.
Methods: We undertook a multi-center single arm Phase II trial to assess the safety and efficacy of PLD 35 mg/m^2 in combination with cyclophosphamide 600 mg/m^2 every 3 weeks. Eligibility criteria included: Measurable disease, prior anthracyclines exposure > 12 months prior to study entry, adequate organ and bone marrow function.
Results: Fifty-one patients have been enrolled, median age 53 years old (38–77). All patients had previously receive anthracyclines either doxorubicin (64%) or epirubicin (36%) at a median dose of 240 mg/m^2 or 600 mg/m^2, respectively. Some patients also received cyclophosphamide (83%), 5-Fu (30%) and taxanes (20%) as part of their adjuvant therapy. A median of 6 cycles (2–10) of chemotherapy were delivered and no major toxicity has been reported after the first 40 patients. Four patients experience asymptomatic >10% declines in LVEF that was reversible upon discontinuation of PLD. The incidence of hand foot syndrome (HFS) was relatively low (13%); only one patient stopped therapy due to grade 3 HFS. Other toxicities were uncommon and usually did not lead to discontinuation